Survival and Health-Related Quality of Life after Hospitalization for Necrotizing Soft Tissue Infections of the Upper Extremity: A Long-Term Outcome Study

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Abstract

Introduction The main aim of the study was to investigate the survival and health-related quality of life (HRQoL) after hospitalization for necrotizing soft tissue infections (NSTIs) of the upper extremity.

Materials and Methods A retrospective study with long-term follow-up of patients surviving NSTIs of the upper extremity was performed. Survival and HRQoL after hospital discharge were the primary outcomes. The HRQoL was measured using the 36-item Short Form (SF-36), EuroQoL-5D-5L (EQ-5D), Quick Disability of Shoulder, Arm and Hand (QuickDASH), and numeric rating scales (NRS) for satisfaction with appearance and pain.

Results A median of 6.5 years after hospitalization, 81% of the 108 patients survived. The response rate was 45% (n = 38). The SF-36 score was 80 (interquartile range [IQR]: 58–91), the EQ-5D score 1.4 (IQR: 1.2–2.2), the EuroQoL-Visual Analog Scale score 77 (IQR: 67-90), the QuickDASH score 13.6 (IQR: 2.3-30.7), the NRS for satisfaction with appearance 8 (IQR: 7–9), and NRS for pain 1 (IQR: 0-5).

Conclusion Six-and-a-half years after the NSTI, 81% of the patients were still alive. General health prior to the NSTI mainly influenced the risk at secondary mortality. In surviving patients, the HRQoL varied widely, but was adversely affected by female sex, intravenous drug use, NSTI type I or III, and longer length of hospital stay.

Keywords
- necrotizing soft tissue infection
- necrotizing fasciitis
- quality of life
- survival
- upper extremity

Introduction

Necrotizing soft tissue infections (NSTIs) are rare, rapidly progressive, and often fatal infections of the fascia and subcutaneous tissues with an estimated incidence in the United States of 4 cases per 100,000 person-years.[1-3] Necrotizing fasciitis, myonecrosis, and necrotizing cellulitis are all NSTI subtypes, of which necrotizing fasciitis is the best known entity and most commonly seen.[1,4] A broad range of microorganisms can cause NSTIs, of which the monomicrobial infection with Group A Streptococcus is most notorious, but NSTIs can also be polymicrobial.[1,5] The exact etiology of NSTIs is not always known, but trauma, intravenous drugs use, animal bites, or surgical complications have frequently been reported as causative events.[1,6] To obtain good clinical outcomes, patients with NSTIs require early recognition, immediate aggressive surgical debridement for source control, and adequate intravenous antibiotics.[7] However, prompt treatment is commonly delayed as a consequence of misdiagnosis.[8] This is due to the diagnostic challenge caused

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by absence of early pathognomonic symptoms for NSTIs.[1,9] Unfortunately, reported mortality rates for NSTIs have not improved over the last two decades and remained stable around 20%.[7] Therefore, the subject of the majority of the available NSTI studies remains the short-term outcomes, such as the mortality and amputation rates.[2,10-12] However, the mortality rate did improve tremendously compared with the rates reported prior to the year 2000.[7] Therefore, the focus should also start to shift toward the quality of life of these patients since such a severe infection requiring highly invasive surgical procedures is likely to adversely affect the quality of life.[13,14] Especially NSTIs of the upper extremity could have even greater (permanent) consequences, since proper upper extremity function has been thought to be essential for maintaining good quality of life due to its major role in self-care and the appearance of the extremity has also been linked to patients' quality of life.[15] Unfortunately, studies specifically assessing the long-term outcomes of upper extremity NSTIs are uncommon, even though prior epidemiology studies have found upper extremity involvement in 7 to 27% of all NSTIs cases and found that especially NSTIs of the upper extremity seem to have a relatively low mortality rate.[4,6,11,16,17] Therefore, the aim of this study is to investigate the survival and health-related quality of life (HRQoL) after hospitalization for NSTIs of the upper extremity and to identify the factors associated with these outcomes.

Materials and Methods

A study protocol was a-priori written; however, it was not registered or published. The institutional review board granted permission for retrospective data collection and the long-term follow-up of patients (IRB #1999P008705). This article was written in adherence to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[18]

Study Design

A retrospective multicenter study with long-term follow-up of patients surviving initial hospitalization for NSTIs of the upper extremity at two urban tertiary referral hospitals was performed from January 1998 to January 2018. Eligible patients were identified from the Institutions' Research Patient Data Registry (RPDR) by using the International Classification of Disease (ICD) 9 (928.86) and ICD 10 (M72.6) code for necrotizing fasciitis. Patients who survived initial hospitalization for NSTIs of the upper extremity were eligible for inclusion. The diagnosis NSTI had to be confirmed based on clinical symptoms and, especially in ambivalent cases, confirmed by pathology (e.g., histology) and/or microbiology (e.g., gram stain or definitive culture) results.[19] Exclusion criteria were age younger than 18 years, pregnancy at time of the NSTI, and death during initial hospitalization for the NSTI. The sample size was determined by the number of eligible patients during the inclusion period and the number of patients willing to participate in the long-term outcome survey.

Explanatory Variables and Outcome Measures

Demographic characteristics collected were age, sex, body mass index, American Society of Anesthesiologists (ASA) classification, comorbidities, medical history, smoking status, history of intravenous drug use, history of opioid abuse, and type of occupation. The disease-related characteristics extracted were time from onset symptoms to diagnosis, affected side, dominant hand, causative event associated with the NSTI, date of causative event, location where symptoms first started, affected body areas, total body surface area (TBSA) affected, the laboratory risk indicator for necrotizing fasciitis (LRINEC) score, upper extremity levels affected by the NSTI, and the microorganism(s) identified. Treatment-related characteristics extracted were the hospital of first presentation, amputation, mortality, date of death, intensive care unit (ICU) admittance, length of ICU and hospital stay, type and number of surgeries performed, date of last surgery for the upper extremity NSTI, infectious complications during admission, and discharge location.

In case of an unreported ASA classification, the ASA classification was determined based on the reported comorbidities at time of admission. Manual laborers were defined as workers mainly doing physical work dominated by grasping and lifting.[20] The TBSA affected was calculated using the rule of nines commonly used in burns.[21] The LRINEC score is a diagnostic score that evaluates sepsis severity and thereby predicts the likelihood of NSTI as diagnosis. The score is based on C-reactive protein, white blood cell count, hemoglobin, sodium, creatinine, and glucose. A LRINEC score <6 represents a low suspicion for a NSTI.[22] The type of NSTI was categorized using the microbiological classification for NSTIs: type I (polymicrobial), type II (monomicrobial), and type III (e.g., *Clostridium* spp. or *Vibrio* spp.).[23]

Survival and HRQoL after hospitalization for NSTIs were the primary outcomes. The survival after hospitalization for NSTIs was determined by the secondary mortality rate, which was defined as death due to any cause after the initial hospitalization for a NSTI. The follow-up period for secondary death was calculated from the date of discharge to October 1st, 2018, which was the date on which mortality data was retrieved from RPDR. HRQoL was measured using the 36-item Short Form (SF-36), EuroQoL-5-Dimensional-5 Levels (EQ-5D-5L) survey, EuroQoL-Visual Analog Scale (EQ-VAS), Quick Disability of Arm, Shoulder and Hand (QuickDASH), numeric rating scale (NRS) for satisfaction with appearance, and NRS for pain. The SF-36 assesses eight different domains: physical functioning, limitations due to physical function, bodily pain, global health perception, vitality, social function, limitations due to emotional health, and general mental health. The higher the score on the SF-36 (ranging from 0 to 100), the better the self-assessed quality of life.[24,25] The eight domains can be split into two subscores ranging from 0 to 50: the Physical Components Summary (PCS) score and the Mental Components Summary (MCS) score.[26] The EQ-5D-5L is a survey with five five-point scale (no problem to unable) questions assessing patient-reported quality of life. The lower the score, the higher the quality

of life. An extension of the EQ-5D-5L is the EQ-VAS, which asks patients to rate their health on a scale from 0 (the worst health imaginable) to 100 (the best health imaginable).[27,28] The QuickDASH assesses the amount of difficulty and symptoms experienced by the patients during daily activities; each question is scored on a scale from 1 (no difficulty or no symptoms) to 5 (unable or severe symptoms). These scores are transformed to a score from 0 to 100, with a higher score indicating worse patient-reported physical arm function and symptoms.[29] The NRS for satisfaction with appearance measures patients' satisfaction with their appearance on a scale from 0 (very unsatisfied) to 10 (very satisfied). The NRS for pain measures a patients' current amount of pain on a scale from 0 (no pain) to 10 (worst pain imaginable).[30]

Patients were contacted by telephone to participate in the survey. To obtain a satisfactory response rate and to reduce nonresponder selection bias, four rounds of phone calls were made at different times of the day.

Statistical Analysis

Continuous parametric variables are presented as means with standard deviations, continuous nonparametric variables as medians with interquartile ranges (IQR), and categorical variables as frequencies and percentages. Missing data were handled using pairwise deletion. Simple logistic regressions were used to identify predictors for secondary mortality. Bivariate analyses, using the Mann–Whitney U test, Kruskal–Wallis test, and Spearman's rank correlation coefficient, were performed to identify associations between the explanatory variables and the survey scores. Multivariable linear regression analyses with backward deletion were used to identify independent predictors for each survey outcome. Variables with a p-value <0.10 in bivariate analyses were imputed in the model. The definitive model consisted of not more than four predictors to prevent overfitting the model. Additional analyses were performed to test generalizability of the results of the responder group to the entire cohort of NSTI patients surviving initial hospitalization. A p-value of <0.05 was considered significant. All analyses were performed with STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, StataCorp LP, Texas, United States).

Results

A total of 108 patients survived initial hospitalization for NSTIs and were included. The short-term, in-hospital outcomes of this cohort were previously published.[6] The mean age was 48 ± 16 years. Most of these patients were classified ASA classification I or II (n = 71, 66%) (►**Table 1**). In most cases, the forearm was affected (n = 83, 77%) (►**Table 2**). Fourteen patients (13%) ultimately underwent an amputation (►**Table 3**).

Survival after Hospitalization

Twenty-one patients (19%) died prior to the start of this study, which corresponds to an 81% survival rate during the median follow-up period of 6.5 years (IQR: 3.7–10.3). The precise date of death was only known of eight patients (38%), those patients died at a median of 18 months (IQR: 2–43) after hospital discharge. Bivariate logistic analyses show that older age at time of the NSTI (odds ratio [OR]: 1.07, 95% confidence interval [CI]: 1.03–1.11), ASA classification III or IV compared with I or II (OR: 4.45, 95% CI: 1.63–12.12), diabetes mellitus (OR: 6.08, 95% CI: 1.94–19.04), a history of malignancy (OR: 5.40, 95% CI: 1.53–19.01), patients who were retired or unemployed (OR: 4.57, 95% CI: 1.60–13.05), type III NSTIs (OR: 10.43, 95% CI: 2.33–46.70), amputation as management for the NSTI (OR: 3.95, 95% CI: 1.20–13.03) and discharged to a rehabilitation facility (OR: 4.96, 95% CI: 1.79–13.74) increased the risk at dying secondarily. Patients who were manual laborers prior to the infection or were discharged home had a lower risk of dying secondarily (OR: 0.22, 95% CI: 0.08–0.63 and OR: 0.21, 95% CI: 0.08–0.59, respectively).

HRQoL after Hospitalization

Eighty-five patients were contacted, of which 38 patients (45%) were willing to participate in the survey (►**Fig. 1**). The median time between discharge and follow-up by survey was 4.7 years (IQR: 3.1–9.4 years). Comparing the responders (n = 38) to the entire cohort of patients surviving initial hospitalization (n = 108), we found that the responders were more often diagnosed with diabetes mellitus (p = 0.009), smoked less often (p = 0.020), had less frequent a history of intravenous drug use (p = 0.049), were more often employed (p = 0.002), and were more often discharged home than to a rehabilitation facility (p = 0.039).The median overall SF-36 score was 80.0 (IQR: 58.2–91.1) (►**Table 4**). Patients scored lowest on vitality (median 65, IQR: 50–75) (Supplementary Table S1, available in the online version). Factors associated with a lower SF-36 score in bivariate analyses were a history of intravenous drug use (p = 0.009) and a longer length of hospital stay (p = 0.039). Multivariable analysis showed that a history of intravenous drug use (β =–32.78; p <0.001) and a longer length of hospital stay (β =–0.39; p = 0.036) were both independently associated with a lower overall SF-36 score (►**Table 5**).

The overall median EQ-5D-5L score was 1.4 (IQR: 1.2–2.2) (►**Table 4**). Patients scored highest on questions about pain and discomfort (median 2 [IQR: 1–3]) (►**Supplementary Table S2**, available in the online version). Factors associated with a higher EQ-5D-5L score (worse HRQoL) in bivariate analyses were a history of intravenous drug use (p = 0.015) and a higher LRINEC score (p = 0.028). Multivariable analysis showed that only a history of intravenous drug use (β = 1.51; p = 0.001) was independently associated with a higher score on the EQ-5D-5L and thus lower quality of life (►**Table 5**).

Patients reported a median score of 77 (IQR: 67–90) on the EQ-VAS (►**Table 4**). Factors associated with a lower EQ-VAS (lower HRQoL) in bivariate analyses were a history of intravenous drug use (p = 0.048), a history of opioid abuse (p = 0.031), an open traumatic wound as causative event (p = 0.042), NSTIs not originating from the upper extremity (p = 0.032), NSTIs that spread to other body regions besides the upper extremity (p = 0.039), NSTIs with involvement of the hand (p = 0.010), and sepsis during hospitalization for the

Table 1 Patient demographic of patient surviving initial hospitalization for necrotizing soft tissue infections of the upper extremity

	Patient surviving initial hospitalization, *n* = 108 (100%)	Patients deceased during follow-up, *n* = 21 (19%)	OR (95% CI)	Patients with long-term follow-up, *n* = 38 (45%)
Age in years, mean ± SD	48 ± 16	62 ± 15	**1.07 (1.03–1.11)**	47 ± 14
Male, *n* (%)	59 (55)	13 (62)	1.45 (0.55–3.84)	20 (53)
BMI in kg/m^2,[a] median (IQR)	25 (23–31)	26 (21–32)	1.00 (0.93–1.07)	24 (22–28)
ASA classification, *n* (%)				
I–II	71 (66)	8 (38)	RC	28 (74)
III–IV	36 (34)	13 (62)	**4.45 (1.63–12.12)**	10 (26)
Diabetes mellitus, *n* (%)	16 (15)	8 (38)	**6.08 (1.94–19.04)**	1 (3)
History of malignancy, *n* (%)	12 (11)	6 (29)	**5.40 (1.53–19.01)**	3 (8)
Smoker at time of NSTI, *n* (%)	39 (36)	5 (24)	0.48 (0.16–1.43)	8 (21)
History of intravenous drug use, *n* (%)	33 (31)	3 (14)	0.31 (0.08–1.14)	7 (18)
History of opioid abuse,[b] *n* (%)	24 (23)	1 (5)	0.13 (0.02–1.03)	5 (14)
Occupation at time of onset NSTI,[b] *n* (%)				
Manual laborer	19 (18)	2 (10)	**0.22 (0.08–0.63)**	4 (11)
Occupation without manual labor	40 (39)	4 (19)	0.33 (0.10–1.07)	23 (62)
Retired or unemployed	44 (43)	15 (71)	**4.57 (1.60–13.05)**	10 (27)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; IQR, interquartile range; NSTI, necrotizing soft tissue infection; OR, odds ratio; SD, standard deviation; RC, reference. Missing case: [a]14 missing; [b]5 missing. **Bold** font indicates significant results.

NSTI (p = 0.027). Multivariable analysis showed that history of intravenous drug use (β =–18.18; p = 0.048), history of opioid abuse (β =–19.57; p = 0.031), and a longer length of hospital stay (β =–0.66; p <0.001) were independently associated with a lower score on the EQ-VAS (►**Table 5**).

The median score on the QuickDASH was 13.6 (IQR: 2.3–30.7) (►**Table 4**). Factors associated with a higher QuickDASH score in bivariate analyses were the type of NSTI (p = 0.029), more NSTI-related surgeries (p = 0.025), more reconstructive surgeries (p = 0.026), longer time between onset of the NSTI and the last surgery (p = 0.013), longer length of ICU stay (p = 0.028), and longer length of hospital stay (p = 0.034). Multivariable analysis showed that factors independently associated with higher DASH scores were type I or type III NSTIs compared with type II (β = 15.32; p = 0.025) and a longer length of hospital stay (β = 0.48; p = 0.003) (►**Table 5**).

The mean score for satisfaction with appearance was 8 (IQR: 7–9) (►**Table 4**). Factors associated with less satisfaction with appearance in bivariate analyses were being a smoker at the time of onset of the NSTI (p = 0.039), history of intravenous drug use (p = 0.016), and ICU admittance (p = 0.030). Multivariable analysis showed that female sex (β =–1.89; p = 0.021) and a history of intravenous drug use (β =–4.78; p = 0.015) were independently associated with lower satisfaction with appearance (►**Table 5**).

The median pain score at long-term follow-up was 1 (IQR: 0–5) (►**Table 4**). Factors associated with more pain in bivariate analyses were female sex (p = 0.033) and the type of NSTI (p = 0.041). Multivariable analysis showed that female sex (β = 1.55; p = 0.035) and type I or III NSTIs compared with type II (β = 3.06; p = 0.004) were independently associated with higher pain scores (►**Table 5**).

Discussion

This study assessed the long-term outcomes of NSTIs of the upper extremity after successful discharge from the hospital. In surviving patients, the HRQoL, function, pain, and satisfaction with appearance scores after NSTIs of the upper extremity were highly variable.

In total, 19% of the NSTI patients died during the follow-up interval of 6.5 years after hospital discharge, while the average age of this population was 48 years. Worse health at baseline (e.g., ASA III or IV, diabetes mellitus, history of malignancy) appears to not only predict the risk at short-term mortality but also predict an increased risk at early mortality after hospital discharge.[5,6] Light et al reported an even higher rate of secondary mortality in a NSTI cohort without limitation on body region. They found a 25% mortality rate within the first 3.3 years after hospital discharge, which increased with the number of comorbidities and age.[13] They found that the cause of secondary death was more common infection-related compared with the cause of death in the general population (14 vs. 2.9%).[13] The phenomenon of a high secondary mortality is also seen in other populations with critical illnesses.[31] For example, a mortality rate of 50% was seen in ICU patients within the first 10 years after hospital discharge.[32]

The HRQoL after NSTIs has only been assessed in four prior studies (one qualitative and three quantitative studies

Table 2 Disease-related characteristics of patient surviving initial hospitalization for necrotizing soft tissue infection of the upper extremity

	Patient surviving initial hospitalization, *n* = 108 (100%)	Patients deceased during follow-up, *n* = 21 (19%)	OR (95% CI)	Patients with long-term follow-up, *n* = 38 (45%)
Affected side, *n* (%)				
Left	55 (51)	11 (52)	0.98 (0.37–2.54)	21 (55)
Right	49 (45)	10 (48)	1.03 (0.39–2.68)	16 (42)
Bilateral	4 (4)	0 (0)	NC	1 (3)
Dominant hand affected,[a] *n* (%)	50 (56)	11 (61)	1.69 (0.99–2.88)	18 (47)
Causative event if known,[b] *n* (%)				
Injection (e.g., intravenous drug use, blood drawl)	25 (36)	2 (17)	0.49 (0.13–1.83)	5 (24)
Trauma without open wound	11 (16)	1 (8)	0.35 (0.04–2.84)	3 (14)
Open traumatic wound	20 (29)	5 (42)	1.50 (0.48–4.73)	10 (48)
Bite (e.g., bug, cat, human)	10 (15)	3 (25)	1.20 (0.23–6.26)	3 (14)
Prior surgery	3 (4)	1 (8)	2.13 (0.18–24.61)	0 (0)
Days between causative moment and diagnosis,[c] median (IQR)	4 (3–8)	6 (3–12)	1.03 (0.94–1.13)	3 (3–5)
Upper extremity not as origin of first symptoms, *n* (%)	2 (2)	0 (0)	NC	36 (95)
Other body regions affected by the NSTI, *n* (%)	12 (11)	4 (19)	0.43 (0.12–1.59)	4 (11)
Head/neck	2 (2)	0 (0)	NC	1 (3)
Trunk	11 (10)	3 (14)	1.65 (0.40–6.82)	4 (11)
Perineum	0 (0)	0 (0)	NC	0 (0)
Lower extremity	3 (3)	2 (10)	8.95 (0.77–103.83)	1 (3)
Percentage TBSA affected by the NSTI, median (IQR)	4 (3–6)	5 (3–7)	1.02 (0.97–1.09)	4 (3–6)
LRINEC score at presentation,[d] mean ± SD	5 ± 3	4 ± 3	0.86 (0.59–1.25)	5 ± 3
Type of NSTI based on definitive culture,[e] *n* (%)				
Type I	19 (20)	3 (15)	0.66 (0.17–2.54)	3 (9)
Type II	68 (71)	11 (55)	0.41 (0.15–1.13)	28 (85)
Type III	9 (9)	6 (30)	**10.43 (2.33–46.70)**	2 (6)
Levels of upper extremity involved, *n* (%)				
Hand	59 (55)	14 (67)	1.87 (0.69–5.07)	22 (58)
Forearm	83 (77)	18 (86)	2.03 (0.55–7.56)	29 (76)
Upper arm	56 (52)	11 (52)	1.03 (0.40–2.67)	19 (50)
Shoulder	16 (15)	4 (19)	1.47 (0.42–5.12)	7 (18)
Number of upper extremity levels involved, median (IQR)	2 (1–2)	2 (2–3)	1.65 (0.91–2.99)	2 (2–2)
Highest level of upper extremity involved, *n* (%)				
Hand	10 (9)	2 (10)	RC	3 (8)
Forearm	40 (37)	8 (38)	1.00 (0.17–5.65)	15 (40)
Upper arm	42 (39)	7 (33)	0.80 (0.14–4.60)	13 (34)
Shoulder	16 (15)	4 (19)	1.33 (0.20–9.08)	7 (18)

Abbreviations: CI, confidence interval; IQR, interquartile range; LRINEC, laboratory risk indicator for necrotizing fasciitis; NC, not calculable; NSTI, necrotizing soft tissue infection; OR, odds ratio; SD, standard deviation; RC, reference; TBSA, total body surface area. Missing cases: [a]19 missing; [b]39 missing; [c]49 missing; [d]63 missing; [e]12 missing. **Bold** font indicates significant result.

with respectively 4.2, 3.2, 4.1, and 5 years follow-up and similar sample sizes ranging from 19 to 56 participants).[14,33-35] The biggest differences between these studies and ours are either the study design (qualitative versus quantitative) or the study population (NSTI of all body regions vs. upper extremity NSTIs). Pikturnaite and Soldin reported an overall SF-36 score of 65.8, while Gawaziuk et al reported a SF-36 PCS score of 36.7 and a SF-36 MCS score of 44.6.[14,35] Suijker et al found a PCS score of 43.8 and a MCS score of 53.3.[34] The previously reported overall SF-36, PCS, and MCS

Table 3 Treatment-related characteristics of patient surviving initial hospitalization for necrotizing soft tissue infections of the upper extremity

	Patient surviving initial hospitalization, *n* = 108 (100%)	Patients deceased during follow-up, *n* = 21 (19%)	OR (95% CI)	Patients with long-term follow-up, *n* = 38 (45%)
First presentation to outside hospital, *n* (%)	75 (69)	18 (86)	3.16 (0.86–11.58)	23 (61)
Time from onset symptoms to diagnosis in days, median (IQR)	2 (1–4)	2 (0–7)	1.03 (0.94–1.14)	2 (1–3)
Number of total operative procedures for the NSTI, median (IQR)	4 (3–6)	4 (3–5)	0.97 (0.85–1.11)	6 (3–8)
Number of total operative procedures on the upper extremity for the NSTI, median (IQR)	4 (3–6)	4 (2–4)	0.88 (0.73–1.07)	5 (3–8)
Debridement and irrigation procedures, median (IQR)	3 (2–5)	3 (2–4)	0.96 (0.78–1.18)	4 (2–6)
Reconstructive procedures, median (IQR)	1 (1–2)	1 (1–2)	0.83 (0.58–1.17)	2 (1–3)
Type of definitive wound closure,[a] *n* (%)				
Wound closure with sutures	30 (32)	3 (16)	0.33 (0.09–1.25)	13 (41)
Skin graft	48 (51)	12 (63)	1.86 (0.66–5.24)	14 (44)
Flap surgery	8 (8.5)	3 (16)	2.63 (0.57–12.13)	2 (6)
Flap surgery and skin graft	8 (8.5)	1 (5)	1.86 (0.66–5.24)	3 (9)
Time from diagnosis to wound closure in days, median (IQR)	7 (4–12)	5 (3–17)	1.01 (0.96–1.05)	7 (3–11)
Time from onset symptoms to last surgery for the NSTI in weeks, median (IQR)	2 (1–8)	2 (1–8)	1.00 (0.99–1.01)	4 (1–27)
Amputation, *n* (%)	14 (13)	6 (29)	**3.95 (1.20–13.03)**	5 (13)
Level of amputation, *n* (%)				
Digits	6 (43)	1 (17)	0.12 (0.01–1.58)	2 (40)
Forearm	2 (14)	1 (50)	1.40 (0.07–28.12)	1 (20)
Transhumeral	5 (36)	3 (60)	3.00 (0.31–28.84)	2 (40)
Forequarter	1 (7)	1 (100)	NC	0 (0)
Length of hospital stay in days, median (IQR)	15 (10–23)	18 (13–27)	1.02 (1.00–1.05)	14 (9–24)
ICU admittance, *n* (%)	73 (68)	17 (81)	2.35 (0.73–7.61)	26 (68)
Length of ICU stay in days,[b] median (IQR)	4 (2–9)	6 (3–11)	1.02 (0.99–1.06)	5 (1–8)
Infectious complications during hospital course, *n* (%)	59 (55)	14 (67)	1.87 (0.69–5.07)	25 (66)
Sepsis/Toxic shock syndrome	56 (52)	13 (62)	1.66 (0.63–4.41)	24 (63)
Pneumonia	8 (7)	2 (10)	1.42 (0.27–7.60)	2 (5)
Discharge location, *n* (%)				
Home	68 (63)	7 (33)	**0.21 (0.08–0.59)**	29 (76)
Rehabilitation facility	39 (36)	14 (67)	**4.96 (1.79–13.74)**	9 (24)
Transfer to other hospital	1 (1)	0 (0)	NC	0 (0)

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; NC, not calculable; NSTI, necrotizing soft tissue infection; OR, odds ratio. Missing cases: [a]14 missing; [b]13 missing. **Bold** font indicates significant result.

score for NSTIs affecting all body regions are lower than the scores found in our study specifically assessing NSTIs of the upper extremity, which were respectively 80.0, 48.7, and 55.3. Based on this comparison, it could be hypothesized that NSTIs of the upper extremity have less consequences for the eventual HRQoL compared with NSTIs affecting other body regions.[14,35] It is possible that NSTIs of the upper extremity have a more favorable anatomical location for aggressive debridement and reconstruction as needed. This theory is supported by the worse EQ-VAS score measured in this study

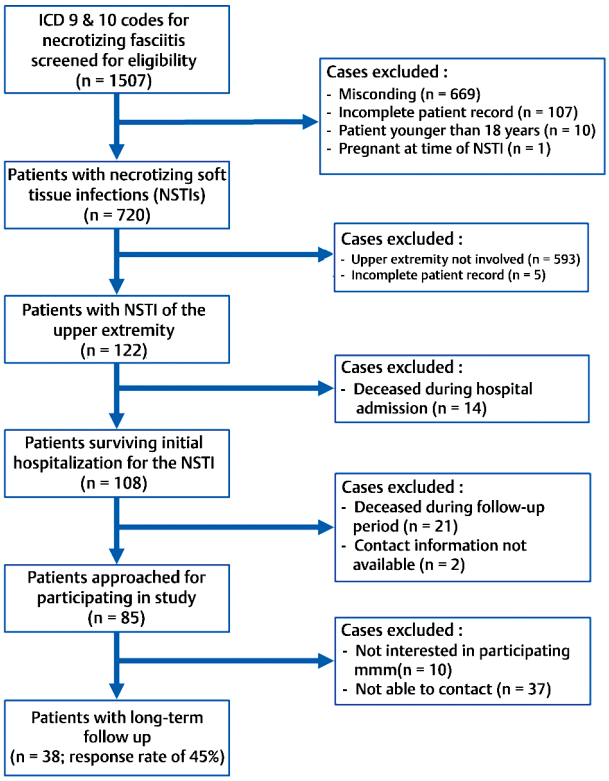

Fig. 1 Flowchart of in- and exclusion of patients with necrotizing soft tissue infections of the upper extremity.

Table 4 Patient-reported long-term follow-up outcome measures of patients with previous necrotizing soft tissue infections of the upper extremity

	Median (IQR)
Years between hospitalization for NSTI and surveys (*n* = 38)	4.7 (3.1–9.4)
SF-36 score (*n* = 38)	80 (58.2–91.1)
PCS score	48.7 (42.2–55.3)
MCS score	55.3 (41.5–57.7)
EQ-5D-5L score (*n* = 38)	1.4 (1.2–2.2)
EQ-VAS (*n* = 36)	77 (67–90)
QuickDASH (*n* = 36)	13.6 (2.3–30.7)
NRS for satisfaction with appearance (*n* = 36)	8 (7–9)
NRS for pain (*n* = 36)	1 (0–5)

Abbreviations: EQ-5D-5L, EuroQoL-5 Dimensional -5 Levels; EQ-VAS, EuroQoL-Visual Analog Scale; IQR, interquartile range; MCS, Mental Components Summary; NRS, numeric rating scale; NSTI, necrotizing soft tissue infection; PCS, Physical Components Summary; QuickDASH, Quick Disability of Arm, Shoulder and Hand; SF-36, 36-item Short Form.

in NSTI patients with the involvement of other body regions besides the upper extremity. However, additional studies would be required to confirm this supposition.

The overall SF-36 score and MCS score in this study are both higher than the estimated scores of the overall US population.[25,26] Mental HRQoL has been related to the level of confidence with appearance, which was scored relatively high in our study, possibly explaining this finding. Nonetheless, the PCS score was lower than the US population score[25,26] Physical HRQoL is mainly related to the TBSA affected by the NSTIs, the remaining amount of pain and energy level.[14,35] Hakkarainen et al performed qualitative interviews with survivors, who also reported that their quality of life was especially affected by ongoing pain and restricted physical function.[33] This is comparable to the results of our surveys, where limitations in physical function and relatively high pain and discomfort scores were frequently reported.

Our cohort consisted of a fairly large number of patients with a history of intravenous drug use, which is not uncommon since intravenous drug use is a known cause of (extremity) NSTIs.[4] Remarkable, patients with a history of intravenous drug use and NSTIs of the upper extremity report worse overall HRQoL. In theory, these patients should have a less complicated disease course since they are often younger, have less comorbidities, require fewer debridements, and have a shorter hospital stay.[36] However, patients with a history of intravenous drug use are also known to have a preexistent lower HRQoL.[37] Unfortunately, we were unable to measure changes in HRQoL, since we could not obtain HRQoL prior to the NSTI due to the acute setting of the infection requiring immediate treatment.

In this study, type I and III NSTIs result in worse functional outcomes and higher pain scores at long-term follow-up. Worse general health and social functioning for type I NSTIs compared with type II NSTIs have previously been reported.[34] Type II NSTIs seem to have a better long-term prognosis compared with type I and III, while it is theorized that the acute phase of type II NSTIs is often more fulminant.[5] A previous study found that involvement of anaerobic bacteria (e.g., *Bacteroides* spp. and *Clostridium* spp.), which is common in type I and III NSTIs, could be associated with an increase in number of surgical revisions.[38] However, the number of reconstructive surgeries and type I or type III NSTIs were both independent variables associated with worse physical function in this study. It is possible that this finding results from a greater difficulty in identifying the required debridement margin caused by a less evident margin between healthy and infected tissue in especially type I and III infection. The differences in microbial etiology have been suggested to cause a different clinical presentation, perhaps also different intraoperative findings.[1] The more favorable long-term functional and pain outcomes achieved in patients with type II NSTIs might also be explained by the fact that these patients are known to be younger and to have less comorbidities, what might contribute to the ability of these patients to rehabilitate better.[1]

The results of this study should be interpreted in the context of its limitations. First, responder bias might be present. Responders with relatively good outcomes after hospitalization might have been more likely to participate. Assessment of the generalizability of the answers of the responders showed that the responders and nonresponders had a comparable disease course, but the responders were overall healthier at baseline. Second, the exact date and cause of death were unknown for most patients, preventing

Table 5 Multivariable linear regression for patient-reported long-term outcome measures in patients with previous necrotizing soft tissue infections of the upper extremity

SF-36	Coefficient β	Standard error	95% CI	*p*-Value
History of intravenous drug use	−32.78	8.23	−49.48 to−16.08	**<0.001**
Longer length of hospital stay	−0.39	0.18	−0.76 to−0.03	**0.036**
EQ-5D-5L				
History of intravenous drug use	1.51	0.35	0.76–2.26	**0.001**
Higher LRINEC score	0.04	0.04	−0.04 to 0.12	0.286
Longer length of hospital stay	−0.01	0.02	−0.05 to 0.02	0.431
EQ-VAS				
History of intravenous drug use	−18.18	8.83	−36.21 to−0.14	**0.048**
History of opioid abuse	−19.57	8.66	−37.26 to−1.88	**0.031**
Sepsis during admission	−10.03	5.67	−21.61 to 1.55	0.087
Longer length of hospital stay	−0.66	0.15	−0.97 to−0.34	**<0.001**
QuickDASH				
Female sex	6.85	4.46	−2.29 to 15.99	0.136
NSTI type I or III compared with type II	15.32	6.44	2.11 to 28.53	**0.025**
Higher number of reconstructive surgeries	1.68	1.06	−0.48 to 3.85	0.122
Longer length of hospital stay	0.48	0.15	0.18 to 0.78	**0.003**
NRS satisfaction with appearance				
Female sex	−1.89	0.78	−3.48 to−0.31	**0.021**
History of intravenous drug use	−4.78	1.86	−8.58 to−0.98	**0.015**
Smoker at time of onset NSTI	2.00	1.74	−1.56 to 5.56	0.261
ICU admittance	−1.89	0.86	−3.30 to 0.20	0.081
NRS for pain				
Female sex	1.55	0.70	0.12 to 2.98	**0.035**
NSTI type I or III compared with type II	3.06	0.96	1.09 to 5.03	**0.004**
Longer time between infection and survey	−0.10	0.08	−0.28 to 0.07	0.225

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQoL-5 Dimensional-5 Levels; EQ-VAS, EuroQoL-Visual Analog Scale; ICU, intensive care unit; LRINEC, laboratory risk indicator necrotizing fasciitis; NRS, numeric rating scale; NSTI, necrotizing soft tissue infection; QuickDASH, Quick Disability of Arm, Shoulder and Hand; SF-36, 36-item Short Form. **Bold** font indicates significant result.

us to draw conclusion about the exact relationship between the previous NSTI and the possible shorted life spam. To understand better which factors predispose secondary mortality after NSTIs and how to prevent it, a prospective study with monitoring of date and cause of death is necessary. Third, the number of patients deceased during the follow-up period might be even larger than presented in this study, since it had to be recorded in our electronic medical record system that the patient was deceased. Finally, this study is limited by the retrospective collection of data on the hospital course. The major strength of this study is that this study is to date the biggest and most detailed study assessing outcomes of NSTIs of the upper extremity after survival of the initial hospitalization and the only NSTI study reporting EQ-5D-5L scores.

Conclusion

We found that worse health at baseline, amputation as management for the NSTI and discharge to a rehabilitation facility were associated with an increased risk of secondary mortality. In surviving patients, the HRQoL, function, pain, and satisfaction with appearance scores after upper extremity NSTIs varied widely, but were adversely affected by female sex, intravenous drug use, NSTI subtype I and III, and longer length of hospital stay.

Note

Informed consent was obtained from all patients for being included in the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

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Conflict of Interest

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